Attorney Docket No.: P-4739-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Moutsatos I. et al.	
SERIAL NO.:	09/148,234	EXAMINER: Riggins,Patrick, R.
FILED:	September 4, 1998	ART UNIT: 1636
FOR:	GENETICALLY ENGINEERED CELLS, WHICH EXPRESS BONE MORPHOGENIC PROTEINS	

For Examiner P. Riggins:
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REQUEST FOR TELEPHONIC INTERVIEW ACCORDING TO 37 CFR 1.133

Further to our telephone conversation of January 10, 2006, please find a summary of issues we raised in our response to the outstanding July 21, 2005 Office Action in connection with the above-referenced file, that we wish to discuss with you.

Pending claims 24-28 (attached hereto as Appendix 1) were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Ahrens further in view of Bonadio et al, and Lee et al.

1-Examiner Alleged:	claims to use of ex-vivo transduced/transfected mesechymal stem cells expressing BMP-2, for inducing organized functional bone formation at a site of bone infirmity is obvious in view of Bonadio, as allegedly Figure 8 of Bonadio shows organized formation at the rejoin of the break.
Applicants Respond:	Figure 8 refers to direct gene transfer experiments for parathyroid hormone gene transfer, and thus do not show organized bone

formation, nor suggest organized bone formation, as a result of transfer of ex-vivo cultured MSC's expressing BMP-2.

Applicants have provided a Declaration, including references to support that Bonadio does not credibly ***specifically target*** progenitor cells using direct gene transfer. Applicants submit that the Examiner has not provided a factual basis for rebutting this contention.

2- Examiner Alleged: Experiments conducted with CHO cells expressing BMP-2 are not appropriate comparison as the state of the art, and represent an "apples and oranges" type argument.

Applicants Respond: CHO cells are an appropriate reference in this context, as they serve as an indication of the contrast between what Bonadio describes and the instant invention. Applicants maintain that the major cell type at a site of bone infirmity taking up a BMP according to Bonadio is a differentiated cell, and not a stem or progenitor cell. Thus, engineered CHO cells express BMP-2, much like the bulk of the cells which are exposed to the BMP construct, following gene transfer experiments as described by Bonadio.

Further, Applicants agree, that expression of BMP-2 from a more differentiated cell type may stimulate "disorganized bone formation" (paragraph 121, Example 11), but not the claimed "organized bone formation". Moreover, bone formation due to expression of BMP-2 from a more differentiated cell type may be short-lived, as 8 weeks after implant, bone resorption is seen in CHO- but not MSC-expressing BMP-2 cells.

3-Examiner Alleged: there is nothing allegedly unexpected in the present study.

Applicants Respond: Implantation of an enriched MSC population expressing BMP-2 promoted organized bone formation, within the boundaries of the fracture edges, and no bone resorption was observed. This is an unexpected finding in view of any of the references cited, alone or in combination.

4-Examiner Alleged: that "the methods of Bonadio alone teach that organized bone formation is achieved. This is evidenced by Fang (PNAS USA 93: 5753-5758 (1996) of record) who teaches that when using the methods of Bonadio, organized bone repair is achieved"... since Bonadio's method leads to organized bone formation, what would lead the skilled artisan to any conclusion other than the reasonable expectation that he combined teachings of Ahrens, Bonadio and Lee would have led to organized functional bone repair?"

ApplicantsRespond: this contention is false:

1) Fang describes use of BMP-4 and not BMP-2.
2) Fang specifically notes that fibroblasts express the BMP-4, following direct gene transfer at the site!

Fang describes a cell type presumptive of being an osteoblast also at the site, and not expressing the BMP, but responding to expressed BMP from the fibroblast! Thus Fang supports Applicants contention that ***Bonadio serves exclusively to highlight contributions of paracrine effects on bone formation***, i.e., gene transfer to differentiated cells, which secrete the BMP, in a limited fashion can

promote osteoblast recruitment and some bone formation at the site, and shows that Bonadio's direct gene transfer experiments do not specifically target uptake by stem or progenitor cells. Moreover, bone formation in Fang and in Bonadio begins in the center and radiates outward, as opposed to the natural course of events in healing fractures, where bone is formed along the defect edge radiating inward, and as occurs with the methods of the subject Application.

5- In summary, Applicants maintain that paracrine effects of BMP-2, as described in Bonadio and Fang, are not sufficient to promote organized bone formation and prevent bone resorption at the site of a bone infirmity. Nor does the combination of Bonadio, Fang, Ahrens or Lee lead one to the unexpected finding that an enriched population of MSCs expressing BMP-2 are particularly useful in promoting organized functional bone, by a process mimicking that which occurs in spontaneously healing bones, and producing qualitatively and quantitatively better bone than that achieved with delivery of the BMP via paracrine effects alone.

6- Applicants maintain that in view of points 1-8, further consideration in view of Wozney or Hattersley do not render the claims obvious, for the reasons stated of record.

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Appendix 1:

Pending Claims:

24. (Previously Presented) A method of inducing organized, functional bone formation at a site of bone infirmity in a human, comprising the steps of:

(a) transforming a cultured mesenchymal stem cell with a DNA encoding bone morphogenesis protein 2 (BMP-2);

(b) culturing the cultured mesenchymal stem cell transformed in step (a), under conditions enabling expression of said DNA encoding bone morphogenesis protein 2; and

(c) implanting said cultured mesenchymal stem cell at a site of bone infirmity

whereby autocrine and paracrine effects of expressed bone morphogenesis protein 2 at said site of bone infirmity result in organized, functional bone formation, thereby inducing organized, functional bone formation at a site of bone infirmity.

25. (Previously Presented) The method of claim 24, wherein said mesenchymal stem cell is a primary cell.

26. (Previously Presented) The method of claim 24, wherein said mesenchymal stem cell is a cultured cell line.

27. (Previously Presented) The method of claim 24, wherein said mesenchymal stem cell expresses an endogenous bone morphogenesis protein receptor.

28. (Previously Presented) The method of claim 24, wherein said mesenchymal stem cell expresses parathyroid hormone and a parathyroid hormone receptor protein.